II. REMARKS

Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

Claim Status

Claims 5-6, 9-10, 14-15, 18-19, and 22-27 were previously cancelled without prejudice or disclaimer.

Claim 7 is being amended to direct the claim to a pharmaceutical dosage comprising an effective amount of DMXAA or the pharmaceutically acceptable salt thereof and an effective amount of gemcitabine for treating a solid cancerous tumor. No new matter is added by the amendments. Support for the amendment to claim 7 can be found, for example, at page 17, lines 5-18 of the instant specification as filed.

Claim 8 is amended for proper antecedent basis.

Claim 12 is being amended for proper claim construction by substitution of the term "the" for "A".

Entry of the amendment is respectfully requested. The amendments are made in a sincere effort to place the claims in condition for allowance or in better form for consideration on appeal and do not require an additional search of the art. The amendments were not made earlier as it was Applicant's belief that the claims as previously presented defined patentable subject matter.

This amendment adds, changes and/or deletes claims in this application. A detailed listing of all claims that are, or were, in the application, irrespective of whether the claim(s) remain under examination in the application, is presented, with an appropriate defined status identifier.

After amending the claims as set forth above, claims 1-4, 7-8, 11-13, 16-17, and 20-21 are pending in this application.

Priority

Applicants thank the Office for acknowledging the submission of the priority document on August 20, 2008.

Information Disclosure Statement (IDS)

Applicants thank the Office for acknowledging the Information Disclosure Statements submitted on August 20, 2008, September 4, 2008 and December 3, 2008.

Applicants also thank the Office for pointing out that the references DE 19721211Al and DE 2015265Al cited as references Fl and F2 in the IDS filed on August 20, 2008, were not considered since the references are not in English and no translation was provided.

Applicants submit concurrently herewith an IDS submitting English translation of DE 19721211Al and DE 2015265Al.

Applicants also thank the Office for pointing out that reference D28 cited on the IDS filed August 20, 2008 was not considered since no publication date was provided.

Applicants submit concurrently herewith an IDS resubmitting D28 with the publication date.

Claim Rejections under 35 U.S.C. § 112, Second Paragraph

Applicants thank the Office for withdrawing the rejection of claims 1-4, 7-8, 11-13, 16-17 and 20-21 under 35 U.S.C. §112, second paragraph.

Claim Rejections under 35 U.S.C. § 103

Applicants thank the Office for withdrawing the rejection of claims 1-4, 7-8, 11-13, 16-17 and 20-21 under 35 U.S.C. §103(a) as allegedly unpatentable over Davis (WO 00/48591).

The Office has maintained the rejection of Claims 1-4, 7-8, 11-13, 16-17 and 20-21 under 35 U.S.C. §103(a) as allegedly unpatentable over Siemann et al. (*Proceedings of the American Association for Cancer Research*, 2000, Vol. 41, page 525) and Pruijn et al. (*Cancer Chemother.*

Pharmacol., 1997, col. 39, pages 541-546) in view of Grindley et al. (U.S. Patent No. 5,464,826) and van Moorsel et al. (*Biochemical Pharmacology*, 1999, Vol. 57, pages 407-415).

The Office alleges that Siemann et al. teach a combination of DMXAA with cisplatin and cyclophosphamide; Pruijn et al. teach a combination of DMXAA with melphalan; Grindley et al. teach gemcitabine as being an anticancer agent; and van Moorsel et al. teach combination of gemcitabine and etoposide.

The Office further alleges that the motivation to pick gemcitabine comes not from Siemann et al. or Pruijn et al. but from Grindley et al. and van Moorsel et al. who teach that gemcitabine is a known anticancer agent that has been combined with other anticancer agents for the treatment of cancer. See page 8, ¶1 of Office Action dated December 22, 2008. The Office further alleges that one skilled in the art of chemotherapy would expect that two agents which are known to be effective to treat cancer as individual agents would also be effective when administered in combination and that the Applicants have presented no evidence to rebut this natural presumption, whereas the art cited by the Examiner supports this presumption of effectiveness. See page 9, ¶2 of Office Action dated December 22, 2008.

Applicants traverse the rejection because the cited art, when combined with the knowledge of skill in the art, fails to teach or suggest the claimed invention. In support of their position, Applicants direct the Office to the Federal Circuit's decision, *Takeda Chem. Indus. Ltd. v. Alphapharm Pty. Ltd.*, 492 F.3d 1350, 83 USPQ2d 1169 (Fed. Cir. 2007), *cert. denied*, wherein the claimed 5-ethyl substituted pyridyl containing compound was held non-obvious over the closed prior art compound, a 6-methyl substituted pyridyl containing compound, when combined with the knowledge available to the skilled artisan at the time the invention was made. Defendants *Alphapharm* sought to invalidate the claimed compound on the ground that one of skill in the art would have been motivated to select the 6-methyl pyridyl containing compound (short handedly referred to as "compound b") as a lead compound for further modification to arrive at the claimed compound. Having selected compound b as the lead compound, one of ordinary skill in the art would have made two obvious changes: homologation (replacing the

methyl group with the ethyl group) and ring walking or moving the substituent from the 6-position on the lead to the 5-position on the claimed compound.

The district court disagreed with defendants *Alphapharm*, and the Federal Circuit agreed and affirmed. In reaching its decision, the district court did not find in the art that suggestion or motivation to select compound b as the lead from the nine disclosed in the prior art to be superior to known compounds. The defendants pointed to a statement in the prior art that characterized compound b as especially important. The court, however, found that this suggestion was negated by the teachings of a separate reference teaching undesirable side effects for compound b. The teachings of the reference were supported by the deposition testimony of defendant's own witness. The court also noted that the claimed compound exhibited unexpected efficacy without the toxicity experienced with the prior art compound b. In sum, the district court and the Federal Circuit affirmed the finding that the prior art as a whole must motivate one of skill in the art to make the modifications of the prior art teachings and such a *prima facie* case can be rebutted by a showing of unexpected results.

Applicants submit that the Office has failed to identify any motivation that would have led a skilled artisan to combine the cited art in a manner to achieve the claimed invention. There are various anticancer agents known in the art and the prior art does not teach that gemcitabine will provide the same or better therapeutic results when combined with any second therapeutic agent. For example, see "Phase III study of gemcitabine in combination with Fluorouracil versus gemcitabine alone in patients with advanced pancreatic carcinoma: Eastern cooperative oncology group trial E2297," *J. of Clinical Oncology*, 20(15):3270-3275 (2002) (attached **Exhibit I**); "Chemotherapy for Elderly Patients With Advanced Non-Small-Cell Lung Cancer: The Multicenter Italian Lung Cancer in the Elderly Study (MILES) Phase III Randomized Trial," *Journal of the National Cancer Institute,* 95(5), March 5, 2003 (attached **Exhibit II**); and "A phase II study of raltitrexed and gemcitabine in patients with advanced pancreatic carcinoma," *British Journal of Cancer* 92(3):445-448(2005) (attached **Exhibit III**).

Therefore, there is ample evidence that suggests that the combination of anticancer agents is not successful in spite of the cancer agents being successful individually. Seeing the unpredictability in the field of cancer treatment with combination therapy, a skilled artisan will have no reasonable expectation of success to combine two anticancer agents, namely, DMXAA and gemcitabine, in the manner claimed in the instant invention.

The Office points to Pruijn et al., on page 545, right hand column, last paragraph, "[t]his study demonstrates the potential of DMXAA to induce microenvironmental changes in tumors that can be exploited by bioreductive drugs and other agents with selectivity for hypoxic and/or acidic conditions. See page 4, ¶2 of Office Action dated December 22, 2008.

Applicants point to Yokoi K. et al. *Clinical Cancer Research* 10:2299-2306 (2004) (see **Exhibit IV**) that demonstrates that hypoxia increases resistance of human pancreatic cancer cells to apoptosis induced by gemcitabine. See, e.g., results section of the abstract of Yokoi et al. Therefore, the hypoxic conditions induced by DMXAA, as taught in Pruijn et al., would increase the resistance of the cancer cells to gemcitabine, as taught in Yokoi et al. After reviewing Pruijn et al. and Yokoi K. et al., there will be no reasonable expectation of success to a skilled artisan to use gemcitabine in combination with DMXAA. This also further corroborates Applicants' assertion that two anticancer agents are not expected to be effective in combination therapy by virtue of them being anticancer agents individually.

Regarding the surprising and unexpected results of the claimed invention, Applicants respectfully state that the Office has mischaracterized the results. The Office alleges on page 10, ¶2 of Office Action dated December 22, 2008:

> For example, the tumor volume tripling time for DMXAA alone was 6.0 days and for gemcitabine alone was 13.9 days. When given in combination, the tumor volume tripling time was ">17" days. The Examiner is not persuaded that the tumor volume tripling time for the combined therapy is unexpected, especially in view of the fact that Puijn teaches that DMXAA can enhance the antitumor effect of a chemotherapeutic agent, likely through its inhibition of tumor blood flow which results in the entrapment of the agent caused by falling tumor blood flow.

Firstly, Pruijn et al. teach away from using the combination of gemcitabine with DMXAA by concluding that DMXAA induces conditions that need to be exploited by agents with selectivity for hypoxic conditions. (See Yokoi K. et al. cited above). Secondly, the Office is pointing to "Median" tumor volume tripling times. The column headed "Treated-control" shows the treated minus control tripling time, i.e., the advantage of the drug or drug combination over untreated tumors. See page 33, lines 14-17 of the application as filed. Therefore, volume tripling times (days) for DMXAA alone is 1.1; for gemcitabine alone is 9; and for the combination of gemcitabine with DMXAA is >12. The effect of the combination is greater than each drug alone or combined, thereby showing synergism. This result is even more surprising since gemicitabine is not expected to be effective in hypoxic conditions induced by DMXAA.

Notwithstanding that the data presented in the instant application shows surprising and unexpected results, Applicants provide herein a Declaration by Hakim Djeha (see **Exhibit V**) that shows the surprising and unexpected results of using the combination of DMXAA and gemcitabine for the treatment of lung cancer. The results presented in the instant application and the results presented in the Declaration clearly show surprising and unexpected results in using a combination of gemcitabine and DMXAA for the treatment of solid cancerous tumor.

Thus, similar to the facts of *Takeda, supra.*, Applicants herein provide evidence contradictory to the *prima facie* evidence of record and supplementary evidence of unexpected results of the claimed invention. Accordingly, the prior art as a whole does not teach or suggest the claimed invention and the rejection under 35 U.S.C. § 103 should be withdrawn.

The Office has again cited *In re Kerkoven*, 205 USPQ 1069 (CCPA 1980) and *In re Sernaker*, 702 F.2d 989, 994-95, 217 USPQ 1, 5-6 (Fed. Cir. 1983) in support of its position in rejecting the claims under 35 U.S.C. §103(a). The Office alleges that the Applicants have presented no evidence to rebut the natural presumption that two agents which are known to be effective to treat cancer as individual agents would also be effective when administered in combination.

Applicants have now provided ample evidence that corroborates Applicants' assertion that two anticancer agents are not expected to be effective in combination therapy by virtue of them being anticancer agents individually. Seeing the unpredictability in the field of cancer treatment with combination therapy, a skilled artisan will have no reasonable expectation of success to combine two anticancer agents, namely, DMXAA and gemcitabine, in the manner claimed in the instant invention.

None of the references cited by the Office suggest (expressly or by implication) the combination of gemcitabine with DMXAA. Although all the cited references together may teach the elements of the instant claims, there is no suggestion or motivation to combine the references and arrive at the synergistic combination of DMXAA and gemcitabine of the claimed invention.

Applicants have provided ample evidence that shows that it is not expected to a skilled artisan that the combination of anticancer agents in the treatment of cancer is as effective as anticancer agent alone. Yokoi K. et al. and Pruijn et al., show that gemcitabine is not effective under hypoxic conditions induced by DMXAA. Therefore, a skilled artisan will have no reasonable expectation of success in combining gemcitabine with DMXAA in the manner claimed in the invention. Finally, the instant application and the Declaration provided herein, show the surprising and unexpected results in using the combination therapy of the claimed invention.

In light of the above, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. §103(a).

Applicants believe that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested

III. CONCLUSION

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 23, 2009

By Antoinette F Konski

FOLEY & LARDNER LLP
Customer Number: 38706
Telephone: (650) 251-1129
Facsimile: (650) 856-3710

Antoinette F. Konski
Attorney for Applicant
Registration No. 34,202
Vandana Bansal
Patent Agent
Reg. No.: 54,979